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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/375,246 | 08/16/1999 | MANUEL PERUCHO | P-LJ-3597 | 4823 |

23601 7590 02/13/2003

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|---|---|
| SOUAYA, JEHANNE E | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

DATE MAILED: 02/13/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/375,246 | Applicant(s) Perucho et al. |
|---|---|---|
| | Examiner Jehanne Souaya | Art Unit 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Nov 22, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-11, 13-21, and 23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11, 13-21, and 23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Continued Prosecution Application*

1. The request filed on 11/22/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/375,246 is acceptable and a CPA has been established. An action on the CPA follows.

2. Currently, claims 1-11, 13-21, and 23 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow.

3. Applicant is advised that should claim 9 be found allowable, claim 11 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof (in the instant case, the two claims are identical and both depend from the same independent claim). When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Sequence Listing***

4. The disclosure is objected to because this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. The specification discloses a nucleotide sequence and designates it as SEQ ID NO 1, however a paper copy of the sequence listing as well as computer readable form of the sequence listing are not present in the application. Further, the specification contains a nucleotide sequence (p. 33) which is not designated by a sequence identifier (SEQ ID NO). Applicant must submit a paper copy and a computer readable form of the sequence listing in response to this office action, as well as a statement that such does not enter new matter into the specification. Appropriate correction is required.

***Specification***

5. The disclosure is objected to because it contains (p. 26 of the specification, for example) an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

***Priority***

6. It is noted that the instant application claims priority to provisional application 60/096,828, filed August 17, 1998. The '828 application, does not provide support for the recitation of "genomic damage fraction" nor of "determining the risk of recurrence of colorectal

cancer", therefore, the effective filing date of claims 1-11 is that of the instant application, August 16, 1999. (It is noted that the office action mailed 12/20/2000 rejected claims 1-23 over Arribas et al under 35 USC 102(a), however, with regard to claims 1-11, the rejection was in error, as such claims should have been rejected under 35 USC 102(b). Therefore, the declaration filed 8/3/01, is not sufficient to overcome the rejection with respect to claims 1-11).

***Claim Rejections - 35 USC § 112***

***New Matter***

7. Claims 13, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims recite the following: in claim 13, step c has been amended to recite "occurrence of chromosome 6 gains or chromosome 4 losses"; in claim 17, step d has been amended to recite "chromosome 4 loss"; and claim 19 has been amended to recite "combination of chromosome 6 gains and chromosome 4 losses". Such amendments introduce new matter into the claims because the claims now encompass losses and gains of complete chromosomes, which was not recited in either the specification as filed, or the originally filed claims. Both the specification and claims recite that 'regions" of chromosomes 4 and 6 are lost and gained, respectively, and do not suggest the loss or gain of complete chromosomes.

***Indefinite***

8. Claims 1-11, 13-21 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite as it is unclear whether the claim is directed to screening for determining a correlation between increased or decreased risk of recurrence of colorectal cancer and a greater or lesser GDF value compared to a predetermined GDF, or if the method is to determine if a subject actually has a risk of recurrence of colorectal cancer. Step c is confusing because it states that a GDF greater than a predetermined GDF is indicative of a first clinical outcome and a GDF lesser than a predetermined GDF is indicative of a second clinical outcome, however the claim defines both the first and second clinical outcomes as the risk of recurrence of colorectal cancer, which is not understood. Does this last step require that both a greater and a lesser GDF correlate to a subject being at risk of recurrence of colorectal cancer? If such is the case, the terms "Genomic Damage Fraction" in step b, and predetermined GDF in step c are unclear. The specification defines "Genomic Damage Fraction" (GDF) as the measure of the change in quantity of nucleic acids between non-normal cells and normal cells in an individual (p. 13) and further teaches that a predetermined GDF value is established by measuring the GDFs of a group of individuals with a cancer and correlating this information with actual clinical outcomes. However, from such definitions it is not understood how both an increased and decreased GDF as compared to a predetermined GDF can *both* be indicative of a risk of

recurrence of colorectal cancer. Claim 1 further lacks sufficient antecedent basis for the term "said clinical outcome" as it is unclear which clinical outcome is being referred to, the "first clinical outcome" or the "second clinical outcome".

B) Claim 5 lacks sufficient antecedent basis for the recitation of "the DNA fingerprint bands" as the term "DNA fingerprint bands" does not appear previously in the claim or in claim 1 and thus it is unclear what DNA fingerprint bands are being referred to.

C) Claims 13, 17, and 21 lack sufficient antecedent basis for the recitation of "the AP-PCR DNA fingerprint" as the term "AP-PCR DNA fingerprint" was does not appear previously in the claim and therefore it is unclear what AP-PCR DNA fingerprint is being referred to.

D) Claim 13, in step c, is indefinite in the recitation of "identifying chromosomal regions from AP-PCR DNA fingerprint data of steps a, b, and c..." as step c does not set for a step of "AP-PCR DNA fingerprinting".

E) Claim 14 lacks sufficient antecedent basis for the recitation of "the gain and loss of nucleic acids" as it is unclear if the nucleic acids are the complete chromosomes (4 and 6) or chromosomal regions. As claim 14 no longer provides specific support for "the nucleic acids" it is unclear what 'gains and losses' are being referred to (chromosomal regions or full chromosomes). Furthermore, it is unclear if claim 14 contains a positive process step of determining gain or loss of metastatic cancer cells. The claim compares the gain and loss of nucleic acids in primary cancer and metastatic cells, but neither claim 13 or claim 14 provides a step of determining gain or loss of chromosomal regions for metastatic cancer cells.

F) Claim 15 lacks sufficient antecedent basis for the recitation of "said chromosomal region" as the term "chromosomal region" does not appear in claim 15 or claim 13. Therefore, it is unclear what chromosomal region is being referred to.

G) Claims 15, 16, 18, and 21 are indefinite. Firstly, the recitation of "the blue primer" lacks sufficient antecedent basis as it is unclear which blue primer is being referred to . Secondly, it is unclear whether the SEQ ID NO in parenthesis is the blue primer, or is an example of a blue primer, ie, are there more than one blue primer? This rejection can be easily overcome by reciting instead "using the primer of SEQ ID NO 1".

H) Claim 17 is indefinite in the recitation of "chromosome 4 loss" in step d, as it is unclear if the recitation is meant to recite that the complete loss of chromosome 4 is prognostic of poor survival, or if only a loss in a region of chromosome 4 is prognostic of poor survival. Claims 13, and 19 also recite chromosome 6 gains and/or chromosome 4 losses. These claims are also unclear as to whether such recitation encompasses gains or losses of complete chromosomes or regions of chromosomes.

I) Claim 18 is indefinite. Firstly, it is unclear what clinical outcome is referred to. Claim 17 has been amended and no longer recites "clinical outcome", therefore it is unclear if claim 18 refers to a different clinical outcome or to prognosing survival. If the former is the case, claim 18 fails to further limit claim 17 and lacks sufficient antecedent basis for "the clinical outcome". Secondly, it is unclear how the blue primer and band N are used to prognose a clinical outcome. Is a reduction in the intensity of band N or the lack of band N prognostic of a clinical outcome or

poor survival? The claim does not make clear the relationship between the presence of band N (or lack thereof) and an ability to prognose a clinical outcome or poor survival.

J) Claim 20 is indefinite as it is unclear how the claim relates back to claim 19. For example, it is unclear that the claim further limits claim 19 because claim 19 specifically recites a combination of "chromosome 6 gains and chromosome 4 losses" whereas claim 20 recites generally "the combination of gains and losses according to chromosomal regions". It is unclear if the chromosomal regions are the combination of chromosome 6 gains and chromosome 4 losses, or whether they refer to other chromosomal regions.

K) Claim 21 is indefinite in the recitation of "relevant for colorectal cancer' as it is unclear if the term 'relevant' is meant to signify a cause of colorectal cancer, or simply a region of a chromosome (ie, a chromosome arm, such as 4q) which may contain a gene associated with colorectal cancer, but wherein the whole region may not be statistically linked to colorectal cancer. Further it is unclear if the term "linked" refers to a linkage analysis, or simply to an association.

L) Claim 21 lacks a positive process step relating back to the preamble. The preamble states a method of identifying a genomic region relevant for colorectal cancer, but the last step indicates identifying a genomic region linked to a colorectal cancer gene, therefore it is unclear if the method is drawn to identifying a genomic region relevant for colorectal cancer or to a method of identifying a specific colorectal cancer gene.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Arribas et al (Journal of Clinical Oncology, vol. 15, pp 3230-3240; October 1997).

The claims are drawn to determining the risk of recurrence of colorectal cancer by determining the relative change in quantity of nucleic acids between cancerous and non cancerous cells, determining the Genomic Damage Fragment, and determining the prognosis of the subject according to the subject's GDF. Arribas teaches a method which was used to evaluate the prognostic significance of the relative value of gnomic damage by DNA fingerprinting in colorectal cancer. Arribas teaches a method in which AP-PCR (DNA fingerprinting) was used to determine gains and losses of nucleic acids between colorectal tumor and paired normal tissue (see p. 3231, tumor specimens - col 1; and quantitation of genomic damage, col. 2). Arribas teaches assessing the genomic damage fraction which is the sum of changes in nucleic acids divided by the total number of bands (see col. 2, p 3232). Further, Arribas teaches using the method as a prognostic indicator (p. 3233, col. 2, last para) and teaches using a GDF of .314 as a cutoff value and that GDF values greater than .314, particularly a 10%

increase, indicated a worse prognosis (see p. 3235, cols 1 and 2). Arribas teaches that mean survival time was half in tumors with GDF greater than .314 with respect to tumors with low GDF values (claims 3 and 4). Arribas further teaches that the GDF was especially useful in identifying lymph node negative tumors that are at high risk of recurrence (fig. 3, and p. 3238, col. 2). With regard to claims 7 and 8, Arribas teaches that only sharp spots (qualitative assessment) clearly distinguishable from the background were considered as bands for the assessment of genomic damage. With regard to claim 10, Arribas teaches assessing both the gains and losses of nucleic acids (fig 2). With regard to claims 9 and 11, Arribas teaches separately determining the gains and losses fractions of nucleic acids (p. 3235, col. 2, last sentence).

11. Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Peinudo et al (Proceedings of the National Academy of Sciences, USA. Vol. 89, pp 10065-10069; November 1992).

The claim is drawn to identifying a genomic region relevant for colorectal cancer by generating the AP-PCR fingerprint of non-cancerous cells, primary cancer, and metastatic tumor cells from a subject and identifying genomic regions showing gains and losses of nucleic acids in certain genomic regions thereby identifying a genomic region linked to a colorectal cancer gene. Peinudo et al teach a method of using APPCR to determine allelic losses (p. 10067, col 1) and gains (p. 10068, col. 2) in colorectal cancer (see abstract, and p. 10065, col. 2). Peinudo et al teach taking colorectal tumor samples of which 7 were adenocarcinomas and 6 were metastatic to

the liver, as well as normal colorectal and liver tissue from the same individuals (p. 10065, col. 2, last para). Peinudo further teaches using DNA sequencing, PCR amplification, and RFLP analysis, as well as the chromosomal localization of cloned sequences and southern Blot hybridization (p.10066, col.1), which identified polymorphic sequences which are thought to be linked to one of the tumor suppressor genes involved in colorectal cancer (p. 10068, col. 1, first para). Peinudo further teaches that these polymorphic sequences were localized in chromosome 17.

***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perucho (Genomic Instability and Carcinogenesis, pp 42-45, 1996) in view of Yasuda et al (Genomics, vol. 34, pp 1-8, 1996) (hereinafter referred to as Yasuda).

The claims are drawn to determining whether the likelihood that colorectal cancer will become metastatic, or prognosing survival for a subject with colorectal cancer by determining an AP PCR DNA fingerprint of non cancerous and cancerous cells from a subject, wherein loss of chromosome 4 or/and gain of chromosome 6 is indicative of the likelihood that a colorectal cancer will become metastatic, or loss of chromosome 4 is prognostic of poor survival for the subject.

Perucho teaches that AP-PCR DNA fingerprinting provides a molecular approach for cancer cytogenetics (p. 42). Perucho teaches that the relative extent of genomic damage, consistent gains and losses of sequences from chromosomes, can be assessed by the comparative analysis of the number of changes in AP-PCR fingerprints of tumor cells compared with their respective normal tissues (p. 42). Perucho teaches that using this method, a molecular karyotype (or amplotype) of *metastatic* colon cancer was generated, which showed that gains of sequences in chromosome 6 and losses in chromosome 4 occurred in a majority of tumors. Although Perucho generally teaches assessing gains and losses using AP-PCR DNA fingerprinting in tumors vs. Normal tissue, Perucho does not teach primers used for the assessment of DNA fingerprint analysis. However, Yasuda et al provide the skilled artisan with a specific method as well as primers for DNA fingerprint generation and analysis for chromosomal karyotyping and

cancer. Yasuda et al specifically teach that chromosome assignment of fingerprint bands is essential for molecular karyotyping of cancer by AP-PCR fingerprinting and specifically teaches using both MCG1 and blue primer in a technique for the simultaneous chromosomal assignment of multiple human DNA sequences from DNA fingerprints obtained by AP-PCR (see abstract, and figs 1 and 2). Yasuda teaches a specific method to generate and assess DNA fingerprint bands in cancerous vs normal tissues and Yasuda specifically teach that with just these two arbitrary primers, all chromosomes but 21 and Y were represented by a DNA fingerprint band (Yasuda specifically teaches a "band N" for chromosome 4 generated with the blue primer - see table 2). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the specific method of Yasuda in the generation of the metastatic karyotype generally taught by Perucho as Yasuda specifically teaches how to obtain and assess DNA fingerprint analysis of cancerous vs. Normal tissues using the MCG1 primer and the blue primer. The ordinary artisan would have been motivated to use the specific method of Yasuda in the general method taught by Perucho as Perucho is silent as to how to obtain and assess AP-PCR DNA fingerprint data in cancerous vs. normal tissues. With regard to claims 17 and 18, although Perucho teaches that losses in chromosome 4 were identified in a majority of tumors used for the assessment of a metastatic karyotype or amplotype but does not specifically teach prognosing survival for a subject with colorectal cancer, poor survival is a property of cancer that has metastasized.

14. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peinado et al in view of Yasuda et al (Genomics, vol. 34, pp 1-8, 1996) (herinafter referred to as Yasuda).

The claim is drawn to identifying a genomic region relevant for colorectal cancer by generating the AP-PCR fingerprint, using the blue primer, of non-cancerous cells, primary cancer, and metastatic tumor cells from a subject and identifying genomic regions showing gains and losses of nucleic acids in certain genomic regions thereby identifying a genomic region linked to a colorectal cancer gene. Peinado et al teach (hererinafter referred to as Peinado) a method of using APPCR to determine allelic losses (p. 10067, col 1) and gains (p. 10068, col. 2) in colorectal cancer (see abstract, and p. 10065, col. 2). Peinado et al teach taking colorectal tumor samples of which 7 were adenocarcinomas and 6 were metastatic to the liver, as well as normal colorectal and liver tissue from the same individuals (p. 10065, col. 2, last para). Peinado further teaches using DNA sequencing, PCR amplification, and RFLP analysis, as well as the chromosomal localization of cloned sequences and southern Blot hybridization (p.10066, col.1), which identified polymorphic sequences which are thought to be linked to one of the tumor suppressor genes involved in colorectal cancer (p. 10068, col. 1, first para). Peinado further teaches that these polymorphic sequences were localized in chromosome 17. Although Peinado teaches using the MCG1 primer and KpnX primer in the AP-PCR and does not teach specifically using the Blue primer in the method of AP-PCR fingerprinting, Yasuda teaches using both MCG1 and blue primer in a technique for the simultaneous chromosomal assignment of multiple human DNA sequences from DNA fingerprints obtained by AP-PCR (see abstract, and figs 1 and

2). Yasuda specifically teach with just these two arbitrary primers, all chromosomes but 21 and Y were represented by a DNA fingerprint band. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the blue primer as taught by Yasuda, in the method of Peinado, for the obvious improvement of obtaining a representation of as many chromosomes as possible in the method of Peinado (it is noted that Peinado is silent as to which chromosomes are represented by the primers used in the method of Peinado). The ordinary artisan would have been motivated to use the blue primer of Yasuda to obtain chromosomal representations that would not be possible with the MCG1 primer of Peinado, and would have recognized that the method of Peinado would be more complete if as many chromosomes as possible were represented in the method of Peinado to detect chromosomal regions of gains and loss associated with colorectal cancer.

***Conclusion***

15. No claims are allowable over the cited prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
1/7/03